A DERIVATION OF THE DISTRIBUTION OF THE INDIVIDUAL BIOEQUIVALENCE METRIC

Sanford Bolton, M. Mohan Sondhi, and Charles Diliberti

The bioequivalence metric as defined by Hyslop is:

$$\phi = [(\mu_t - \mu_r)^2 + \sigma_i^2 + 0.5\,\sigma_t^2]/\sigma_r^2 - 1.5.$$

where μ_t, μ_r are the means of the pharmacokinetic parameter for the test and reference products, respectively

σ_t^2, σ_r^2 are the within-subject test and reference variances,

σ_i^2 is the variance of $(\mu_t - \mu_r)$.

Let $\bar{X}_t$, $\bar{X}_r$, S_i^2 , S_t^2 , and S_r^2 be the sample estimates of μ_t, μ_r, σ_i^2, σ_t^2, and σ_r^2, respectively, and let $\hat{\phi}$ be the sample estimate of ϕ derived from them.

The problem is to find the 95th percentile of the probability distribution of $\hat{\phi}$ and accept bioequivalence if this value is below the FDA specified value

Hyslop *et al* find the upper 95% confidence interval of a linearized version of the metric

We, instead, find the probability density function (pdf) of $\hat{\phi}$, whose integral gives us the cumulative distribution

If the 95% point of the cumulative distribution is below the FDA defined value we accept bioequivalence

- The PDF of $\hat{\phi}$ can be determined if the joint distribution of $\bar{X}_t$, $\bar{X}_r$, S_i^2 , S_t^2 , and S_r^2 is known.
- In general this would be a formidable task.
- However, under the usual assumption of statistical independence of these variables, the computation is quite feasible.
- The main steps in the derivation are summarized in the next two vugraphs.

For ease of notation define the following random variables:

$$Y = (\bar{X}_t - \bar{X}_r)^2,$$
$$Z = S_i^2,$$
$$U = 0.5\, S_t^2,$$
$$V = S_r^2.$$

In terms of these, define the further intermediate variables

$$W = Y + Z$$
$$G = W + U.$$

Then the random variable $\hat{\phi}$ is given by

$$\hat{\phi} = \frac{G}{V} - 1.5.$$

- A knowledge of the PDF of $\bar{X}_t$ and $\bar{X}_r$ (assumed gaussian), gives the PDF of Y

  (Need formula for the PDF of the square of a random variable)

- Next compute the PDF of W

  (Need formula for the PDF of the sum of two independent random variables)

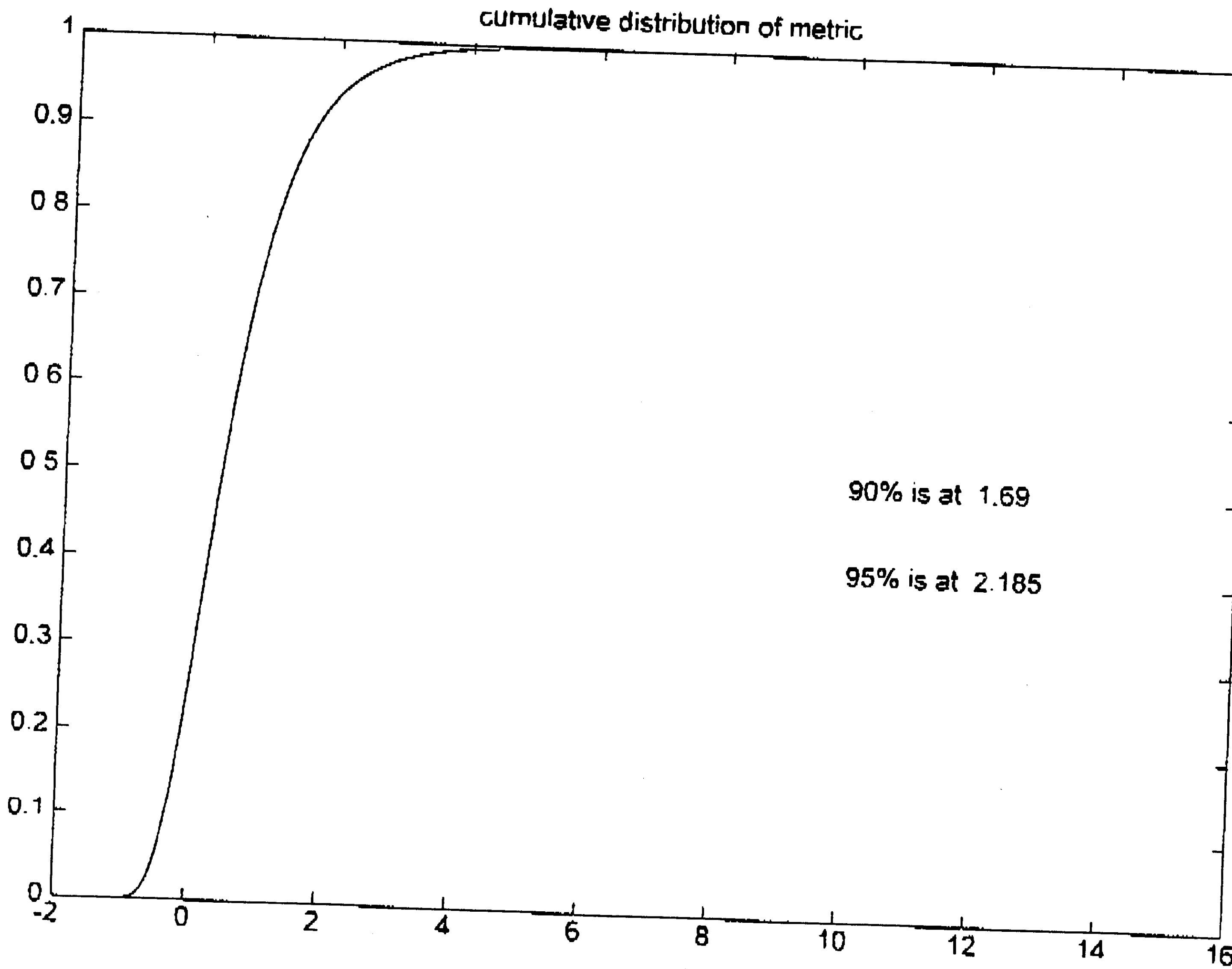
- Similarly compute the PDF of $G = W + U$.
- Next compute the PDF of G/V

  (Need formula for the PDF of the ratio of two independent random variables)

- Finally, shift the PDF of G/V by 1.5 to get the PDF of $\hat{\phi}$.

Table I. Comparison of Results of Proposed Method to Hyslop's method for assessing bioequivalence for various parameter estimate values.

N[a]	Mean Diff	S^2I	S^2t	S^2r	Hyslop	Proposed
122	0.0	0.02	0.02	0.0125	-0.0286(**P**)	1.635(**P**)
	0.0	0.02	0.02	0.01	-0.0007(**P**)	2.46 (**P**)
	0.0	0.02	0.03	0.01	+0.0046(**F**)	2.79 (**F**)
	0.2	0.12	0.12	0.065	+0.0226(**F**)	2.90 (**F**)
12	0	0.04	0.02	0.0475	-0.0324(**P**)	1.69 (**P**)
	0.05	0.03	0.01	0.03	-0.0087(**P**)	2.295(**P**)
	0	0.05	0.04	0.0475	+0.0004(**F**)	2.85 (**F**)
	0.07	0.05	0.04	0.0475	+0.0082(**F**)	3.175(**F**)


cumulative distribution of metric
90% is at 1.69
95% is at 2.185
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
-2
0
2
4
6
8
10
12
14
16